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Full coverage for preventive medications after myocardial infarction

Choudhry *et al.*, *N Engl J Med* 2011; **365**: 2088–2097; doi:10.1056/NEJMsa1107913

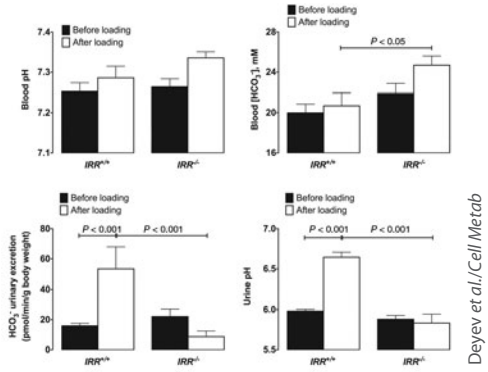
Health-care providers to patients with end-stage renal disease (ESRD) are under increasing financial pressure to be as cost effective as possible with respect to the choice of medications. Factors affecting medication adherence are not well defined in the ESRD population, so evaluation of the literature on patients with normal kidney function may provide insight. Choudhry *et al.* performed the Post-Myocardial Infarction Free Rx Event and Economic Evaluation (MI FREEE) trial to assess the impact of oral-medication copayments on outcomes following myocardial infarction (MI). Patients receiving medical and prescription drug benefits through Aetna who were discharged from the hospital with the diagnosis code 410 (the ICD-9 code for MI) were eligible for inclusion. Patients agreeing to participate were randomized either to have their copayments and coinsurance waived for statins, beta-blockers, angiotensin-converting enzyme inhibitors, or angiotensin receptor blockers (the full-coverage group) or to maintain their current level of copay. Medication adherence was assessed by the ratio between the number of days a patient had a supply of each medication and the number of days of eligibility for that medication. The primary outcome was a composite of first readmission for a major vascular event (MI, unstable angina, stroke, or congestive heart failure) or coronary revascularization (coronary bypass, stenting, or angioplasty). Of the 6768 potentially eligible patients, 5855 were enrolled. In general, adherence to medications was relatively low and quite variable in both arms. Absolute adherence to the three classes of medications was 43.9% in the full-coverage group and 38.9% in the usual-coverage group. Notably, the standard deviation for mean adherence was large (33.7% and 32.7%, respectively), suggesting considerable variability in the cohort overall. The full-coverage group consistently had greater adherence with an absolute difference of 5.4% greater adherence (an improvement of 41% in the relative adherence). Although the time to first occurrence of the end point was no different between arms, the total number of events was lower in the full-coverage group (hazard ratio, 0.89). This improvement was driven primarily by significant reductions in MI or unstable angina, and stroke with congestive heart failure and cardiovascular death had non-significant trends in the same direction.

This trial demonstrates that the copay may represent an obstacle to adherence that significantly influences outcomes. Since payment for dialysis may include oral medications, extrapolation of these findings to people with ESRD suggests the possibility that similar improvement in compliance and outcomes may be on the horizon.

Lynda Szczech

A pH-sensing receptor to excrete bicarbonate

Deyev *et al.*, *Cell Metab* 2011; **13**: 679–689; doi:10.1016/j.cmet.2011.03.022



Top: Blood pH and bicarbonate in $IRR^{+/+}$ and $IRR^{-/-}$ mice before and after 7 days of alkali load administered as 0.28 M solution of $NaHCO_3$ in the drinking water. **Bottom:** Initial urinary bicarbonate excretion and urine pH in renal response to alkali loading measured in $IRR^{+/+}$ and $IRR^{-/-}$ mice.

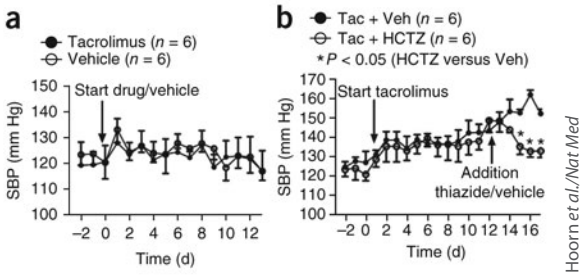
Although the overall responses of an organism to acid or alkali loads are fairly well understood, it remains unclear how cells sense changes in pH. In a recent communication, Deyev *et al.* reported that the insulin receptor-related receptor (IRR) is an extracellular alkali sensor that is critical for the collecting duct response to alkali. IRR is a member of a family of three structurally related receptor tyrosine kinases that includes insulin receptor and insulin-like growth factor receptor. The natural agonists of the latter two are insulin and the two insulin-like growth factors, I and II. None of these ligands activates IRR, and the physiological role of this receptor has remained unknown despite multiple efforts seeking its ligand. Interestingly, IRR is expressed primarily in the kidneys, stomach, and pancreas—organs that have acid- or base-transporting epithelia. However, no overt phenotype was detected in mice with targeted inactivation of the IRR gene. Deyev *et al.* embarked on a search for the endogenous agonist of IRR and found that its activation could be achieved by an increase in extracellular pH. Remarkably, IRR activation by alkaline media was specific, dose dependent, reversible, determined by the receptor ectodomain, and accompanied by a conformational change of the receptor molecule, thus resembling typical features of the ligand–receptor interaction. Further, IRR activation triggered intracellular signaling that involved insulin receptor substrate-1 and AKT/PKB as well as actin cytoskeleton remodeling. Detailed analysis of $IRR^{-/-}$ mice revealed an impaired renal response to alkali loading; the urinary excretion of bicarbonate was decreased, and the animals developed metabolic alkalosis (Figure). Immunoblot analysis of pendrin and of the β1 subunit of the V-H^+-ATPase in the kidney cortex of alkali-loaded $IRR^{-/-}$ and wild-type mice showed that despite the metabolic alkalosis, $IRR^{-/-}$ mice had an approximately 40% decrease in the abundance of both proteins, indicating that

the absence of IRR disrupted the β-intercalated cells of the collecting duct and thereby prevented the tubule's ability to secrete bicarbonate. The study thus shows that IRR acts as a cell-surface alkali-sensing receptor that is involved in the renal adaptation to metabolic alkalosis.

Qais Al-Awqati

Calcineurin inhibitors induce hypertension by activating the renal sodium chloride cotransporter

Hoorn *et al.*, *Nat Med* 2011; **17**: 1304–1309; doi:10.1038/nm.2497



(**a**) Effects of tacrolimus on systolic blood pressure (SBP) of NCC knockout mice. (**b**) Effect of treatment with hydrochlorothiazide (HCTZ) or vehicle (Veh) on established tacrolimus (Tac)-induced hypertension in wild-type mice.

Calcineurin inhibitors (CNIs) are immunosuppressive drugs that revolutionized the practice of organ transplantation. In addition to their use in preventing rejection of transplanted organs, they are also used now to treat autoimmune disease. Excepting nephrotoxicity, the most consistent side effect of therapy with CNI is hypertension, a considerable problem in patients with already significant cardiovascular burden. Interestingly, other side effects of CNI are hyperkalemia, hypercalciuria, and, occasionally, metabolic acidosis. This combination resembles some cases of familial hyperkalemic hypertension (Gordon's syndrome), a genetic disorder characterized by overactivity of the renal sodium chloride cotransporter (NCC) and caused by mutations in genes encoding WNK (with no lysine) kinases. Hoorn *et al.* postulated that CNIs induce hypertension by activating NCC. They found that in wild-type mice, tacrolimus caused salt-sensitive hypertension and increased the abundance of phosphorylated NCC and the NCC-regulatory kinases WNK3, WNK4, and SPAK. The functional importance of NCC in this response was demonstrated by the finding that tacrolimus did not affect blood pressure in NCC knockout mice (Figure), whereas it caused worse hypertension in mice overexpressing NCC. Moreover, hydrochlorothiazide, an NCC-blocking drug, reversed tacrolimus-induced hypertension. Interestingly, in human studies the authors found that kidney transplant recipients treated with tacrolimus had a greater fractional chloride excretion in response to bendroflumethiazide, another diuretic that is an NCC blocker, than people not treated with tacrolimus; moreover, in kidney biopsies of patients receiving CNIs, they found a pronounced increase in NCC and phosphorylated-NCC staining compared with controls. In the aggregate, these results indicate that CNI-induced chronic hypertension is mediated largely by NCC activation and suggest that the best therapy for these patients' hypertension is thiazide diuretics.

Juan Oliver

Loss of function in *DNASE1L3* causes a familial form of SLE with high frequency of nephritis

Al-Mayouf *et al.*, *Nat Genet* 2011; **43**: 1186–1188; doi:10.1038/ng.975

In combination with environmental factors, genetic determinants have been shown to have an important role in the pathogenesis of systemic lupus erythematosus (SLE), but their exact nature remains poorly understood. In genome-wide association studies and case-control studies using candidate-gene approaches, several risk alleles have recently been identified, and it has been estimated that less than 15% of the heritability of SLE can be explained by known genetic variants. It is likely that the inability to determine much of the heritability of SLE reflects, in part, genetic heterogeneity, as well as researchers' limited ability to 'bin' SLE cases into subgroups that are more homogeneous in their molecular pathology. In an extreme form, this homogeneity would consist of a single genetic etiology that acts in a Mendelian fashion. Al-Mayouf and colleagues postulated that there could be a Mendelian phenocopy for SLE, such that a specific genetic etiology could be identified and investigated in the common form of SLE, thus allowing identification of a subgroup in whom variants of this gene contribute to overall risk. The remarkably high rate of consanguinity in the Arab population made it theoretically probable that at least one autosomal recessive phenocopy of SLE could be identified. In order to enhance their chances of success, the authors screened a cohort with SLE for those with a family history consistent with an autosomal recessive pattern of inheritance; they enrolled only subjects with at least two affected siblings and healthy consanguineous parents. Seven such families were identified and studied. In six families, they found a linkage locus on 3p14.3 with a logarithm of odds (LOD) score of 6.6. This interval contained 206 genes. Among these genes, *DNASE1L3* was considered a prime candidate, because SLE pathogenesis is related to a decrease in the ability to clear DNA released from apoptotic cells, and *Dnase1*-null mice recapitulate the human disease. The protein encoded by *DNASE1L3* is one of three human homologs of DNase I that cleaves both single- and double-stranded DNA. Sequencing of *DNASE1L3* uncovered a homozygous 1-bp deletion in *DNASE1L3* that segregated perfectly with the disease in a strictly Mendelian, fully penetrant, and autosomal recessive fashion in all six families. Additional work provided strong evidence that the mutation is pathogenic, and it was not identified in a panel of 192 control subjects. The *DNASE1L3*-related SLE always started in childhood and correlated with a high frequency of lupus nephritis. This study adds strong confirmation to the critical role of impaired clearance of degraded DNA in SLE pathogenesis.

Juan Oliver